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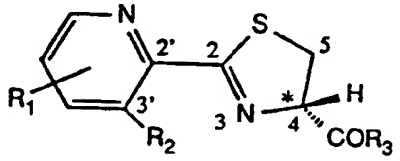
(54) Title: 2-(PYRID-2'-YL)-2-THIAZOLINE-4(S)-CARBOXYLIC ACID DERIVATIVES



(I)

(57) Abstract

2-(Pyrid-2'-yl)-2-thiazoline-4-carboxylic acid derivatives of formula (I) in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy or resterified hydroxy; and R_3 represents etherified hydroxy or a group of the partial formula -N(R_4, R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl or in which R_4 represents hydroxy or esterified hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl; and salts thereof form chelate-type metal complexes with trivalent metal ions, especially iron (III), and can be used, for example, for the treatment of pathological conditions in warm-blooded animals that are associated with an excess of trivalent metal ions in the body. Valuable starting material embraces alkali and alkaline earth salts of 2-(3'hydroxypyrid-2'-yl)-2-thiazoline-4(S)-carboxylic acid.

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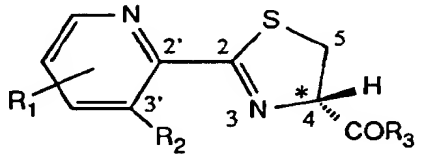
2-(Pyrid-2'-yl)-2-thiazoline-4(S)-carboxylic acid derivatives

The invention relates to novel derivatives of 2-(pyrid-2'-yl)-2-thiazoline-4(S)-carboxylic acid, processes for their manufacture, pharmaceutical compositions containing such compounds, and the use of these derivatives. The invention is also directed to alkali and alkaline earth metal salts of 2-(3'hydroxypyrid-2'-yl)-2-thiazoline-4(S)-carboxylic acid which represent valuable starting material and exhibit valuable therapeutical properties.

The invention relates especially to 2-(pyrid-2'-yl)-2-thiazoline-4(S)-carboxylic acid derivatives of the formula (I)

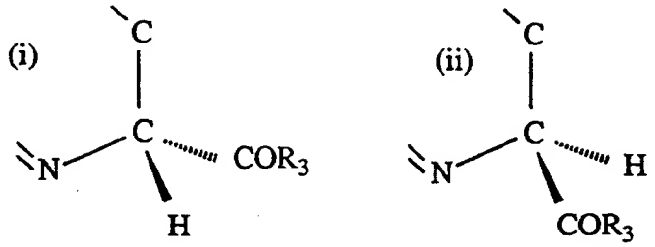


(I),

in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy or esterified hydroxy; and R_3 represents etherified hydroxy or a group of the partial formula -N(R_4,R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl or in which R_4 represents hydroxy or esterified hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl; and salts thereof, processes for the manufacture of these compounds, pharmaceutical compositions containing such compounds and the use of these compounds.

The compounds of the formula (I) are characterized by the asymmetric carbon atom C4 marked with an asterisk. The bonds surround C4 are arranged tetrahedrally, and the substituents are in fixed positions. Thus the compounds of formula (I) represent optical

antipodes exhibiting (S) conformation as shown in example (i) below:



(S) conformation (R) conformation

Contrary to the compounds of the formula (I) according to the present invention, 2-(3'-hydroxypyrid-2-yl)-Δ^2-thiazoline-4(R)-carboxylic acid (desmethyldesferrithiocin), its sodium salt and its methyl ester which are described by Bergeron et al. [Journal of Medical Chemistry, Vol.34, No.7, pp 2072-78 (July 1991)] exhibit the (R) conformation illustrated in example (ii) above. Racemic 2-(3'-hydroxypyrid-2-yl)-Δ^2-thiazoline-4-carboxylic acid and racemic lower alkyl esters thereof are also known and described in U.S. Patent No. 4,406,905.

In contrast to the (R) comformers described by Bergeron et al. and the racemates described in U.S. Patent No. 4,406,905 the present invention is exclusively directed to (3'-hydroxypyrid-2-yl)-Δ^2-thiazoline derivatives showing (S) conformation because it surprisingly was found that the (S) conformers have significant therapeutical advantages over the known compounds.

A therapeutically preferred subgroup within the formula (I) consists of those representatives wherein

(a) R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl;
R_2 represents hydroxy or esterified hydroxy; and
R_3 represents, together with the carbonyl group to which it is attached, an esterified carboxyl group that can be cleaved under physiological conditions or a group of the partial formula -N(R_4,R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl or in which R_4 represents hydroxy or esterified hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl; or

(b) R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl;
R_2 represents esterified hydroxy; and
R_3 represents C_1-C_4 alkoxy; or

(c) R_1 represents halogen, hydroxy or C_1-C_4 alkoxy;
R_2 represents hydroxy; and
R_3 represents C_1-C_4 alkoxy; and salts thereof.
Among this subgroup the (a) type compounds are mostly preferred.

Within the scope of the present description, the definitions used hereinbefore and hereinafter have preferably the following meanings:

Halogen R_1 is, for example, fluorine or chlorine. C_1-C_4 alkoxy is, for example, ethoxy or, especially, methoxy. C_1-C_4 alkyl is, for example, corresponding unbranched alkyl such as ethyl, n-propyl or, especially, methyl. C_1-C_2 alkyl R_6 is especially methyl.

Esterified hydroxy R_2 and R_4 is especially corresponding esterified hydroxy which is cleavable (that is to say metabolisable) under physiological conditions. Such metabolisable esterified hydroxy groups are known in the art. Corresponding esterified hydroxy R_2 or R_4 is, for example, a radical -O-Ac in which Ac represents the acyl radical of a carbonic acid semiester, in particular carbonic acid semi-C_1-C_4-alkyl ester or carbonic acid semi-oxaalkyl ester in which oxaalkyl has 4-13 chain members, such as an acyl radical -C(=O)-(O-CH_2-CH_2)$_n$-O-Alk in which n is an integer from 0 to 4 and Alk represents C_1-C_4 alkyl, in particular methyl or ethyl. Such acyl groups Ac are, for example, methoxycarbonyl, ethoxycarbonyl or 2-(methoxyethoxy)-ethoxycarbonyl. Further acyl radicals Ac are, for example, C_1-C_3 alkanoyl such as acetyl or propionyl, or monosubstituted or disubstituted carbamoyl such as di-C_1-C_4-alkyl carbamoyl, for example dimethylcarbamoyl or diethylcarbamoyl, or C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl-carbamoyl, for example methoxycarbonylmethylcarbamoyl, ethoxycarbonylmethyl-carbamoyl or 2-ethoxycarbonylethylcarbamoyl.

Etherified hydroxy R_3, together with the carbonyl group to which it is attached, forms, for example, C_1-C_4 alkoxycarbonyl or an esterified carboxyl group that can be cleaved under physiological conditions. C_1-C_4 alkoxycarbonyl as group -COR_3 is, for example, corresponding unbranched alkoxycarbonyl such as ethoxycarbonyl, n-propoxycarbonyl or, especially, methoxycarbonyl. Esterified carboxy groups -COR_3 that can be cleaved under physiological conditions are known in the art. Suitable groups are especially C_1-C_4-alkanoyloxymethoxycarbonyl such as acetoxymethoxycarbonyl or pivaloyloxymethoxy-carbonyl, C_1-C_4-alkoxycarbonyloxy-C_1-C_4-alkoxycarbonyl such as methoxycarbonyloxy-methoxycarbonyl or ethoxycarbonyloxymethoxycarbonyl, or 2-oxo-1,3-dioxolen-4-yl-

methoxycarbonyl that is optionally substituted in the 5-position of the dioxolen ring by C_1-C_4 alkyl, for example methyl, or phenyl. A further suitable esterified carboxy group that can be cleaved under physiological conditions is a group $-C(=O)-(O-CH_2-CH_2)_m-O-Alk$ in which m is an integer from 1 to 4 and Alk represents C_1-C_4 alkyl, in particular methyl or ethyl. Such groups are, for example, 2-(methoxy-ethoxy)-ethoxycarbonyl or 2-[2-(methoxyethoxy)-ethoxy]-ethoxycarbonyl.

C_2-C_{12} alkylen X is, for example, corresponding unbranched alkylen such as 1,4-butylen, 1,5-pentylen, 1,6-hexylen, 1,7-heptylen, 1,8-octylen, 1,9-nonylen or 1,10-decylen. Oxaalkylen having 4-12 chain members is, especially, corresponding unbranched (straight-chained) alkylen that is interrupted by 1 to 4 oxygen atoms provided that the individual oxygen atoms are separated from each other by at least two carbon atoms, such as the radical $-(CH_2-CH_2-O)_m-$ in which m is an integer from 1 to 4 and the first CH_2 group is attached to the carboxamide N-atom. Corresponding groups are, for example, dioxyethylene and trioxyethylene.

C_1-C_4 alkanoyl R_7 is, for example, formyl, acetyl or propionyl.

In this description, the term "lower" used in connection with definition of groups and compounds denotes, unless expressly defined otherwise, that the groups or compounds so designated contain from 1 to 7, more especially, from 1 to 4, carbon atoms.

The compounds of the formula (I), for example those in which the radical R_1 and/or R_2 represents hydroxy and/or the radical $-COR_3$ represents a group of the partial formula $-CON(R_4,R_5)$ in which R_4 represents hydroxy and R_5 has the above meanings, are capable of forming salts. The salts of the compounds according to the invention are, especially, pharmaceutically acceptable, non-toxic salts. Such salts are especially metal salts and ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts as well as related 2+ salts such as zinc salts, and ammonium salts with ammonia or suitable organic amines, there coming into consideration for the salt formation especially aliphatic, cycloaliphatic, cycloaliphatic-aliphatic or araliphatic primary, secondary or tertiary mono-, di- or poly-amines, and also heterocyclic bases. Such amines are, for example, lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tris-(2-hydroxyethyl)-amine, basic aliphatic esters of carboxylic acids, for example 4-aminobenzoic acid 2-diethylaminoethyl ester, lower

alkyleneamines, for example 1-ethylpiperidine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzyl-ethylenediamine, also bases of the pyridine type, for example pyridine, collidine or quinoline. Further salts are internal salts (zwitterionic forms of compounds of the invention), wherein a basic group, for example the basic nitrogen atom present in the pyridine ring, is protonated by a hydrogen ion originating from an acidic group in the molecule of the formula (I). The compounds of the formula (I) can also form intermolecular (as opposed to intramolecular, i.e. zwitterionic) acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulphuric acid or phosphoric acid, or with suitable organic carboxylic or sulphonic acids, for example methanesulfonic acid, or with amino acids, such as arginine and lysine.

For isolation and purification, pharmaceutically unacceptable salts also can be used. Only the pharmaceutically acceptable, non-toxic salts are used for therapeutic application and, for that reason, they are preferred.

The compounds of the formula I, for example those having a group of the partial formula $-N(R_4,R_5)$ in which R_4 represents hydroxy and R_5 has the above meanings, are capable of forming stable complexes with metal ions, such as heavy metal ions. Of the heavy metal ions, there may be mentioned especially those in the 3+ oxidation state, such as Al^{3+} or, most especially, Fe^{3+}. Such metal ion complexes are comprised by the term "salts" and are also a subject of the present invention .

The substances of the formula (I) possess pharmacologically valuable properties. Owing to their ability to form stable complexes with heavy metal ions, especially with those in the 3+ oxidation state, such as Al^{3+} or, most especially, with Fe^{3+}, the compounds of the formula (I) having a metabolisable carboxy ester group (R_3 together with the carbonyl group to which it is attached, forms an esterified carboxyl group that can be cleaved under physiological conditions) or a group of the partial formula $-N(R_4,R_5)$ in which R_4 represents hydroxy and R_5 has the above meanings, prevent, for example, the deposition of iron-containing pigments in the tissues and, in cases where iron has been deposited in the organism, bring about elimination of the iron, for example in haemochromatosis and haemosiderosis and also in cirrhosis of the liver. They can also be used for the elimination from the organism of other heavy metals, for example aluminium and also chromium and copper. Thus, the compounds of the formula I can also be used in the case of dialysis encephalopathy, osteomalacia and Alzheimer's disease.

For the purpose of eliminating heavy metal ions, for example iron(III) ions, it is also possible to use compounds of the formula (I) having a suitably esterified phenolic hydroxy group (R_2 is esterified hydroxy and, optionally, R_1 is an esterified hydroxy group) and/or esterified hydroxylamine hydroxyl group (R_4 is esterified hydroxy), the ester grouping(s) of which is (are) readily cleaved under physiological conditions (prodrug forms).

On the other hand, owing to their high solubility and good tolerability, the metal ion complexes of compounds of the formula (I) in which R_1 has the above meanings, R_2 represents hydroxy and R_3 represents a group of the formula -N(R_4,R_5) in which R_4 represents hydroxy and R_5 has the above meanings, especially with suitable paramagnetic and/or radioactive metals, can be used as contrast agents in diagnostic medicine, for example X-ray, radionuclide, ultrasound and/or magnetic resonance diagnostics.

In one preferred embodiment the present invention is directed to compounds of the formula I in which R_3 represents etherified hydroxy or a group of the partial formula -N(R_4,R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl and R_1 and R_2 have the above meanings, and salts thereof.

In another preferred embodiment the present invention is directed to compounds of the formula I in which R_3 represents a group of the partial formula -N(R_4,R_5) in which R_4 represents hydroxy or esterified hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl and R_1 and R_2 have the above meanings, and salts and metal ion complexes thereof.

In particular, the invention concerns compounds of the formula I in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy or esterified hydroxy which is cleavable under physiological conditions; and R_3 together with the carbonyl group to which it is attached, represents esterified carboxy which is cleavable under physiological conditions, and salts thereof.

In particular, the invention concerns also compounds of the formula I in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy or esterified hydroxy which is cleavable under physiological conditions; and R_3 represents a group of the partial formula -N(R_4,R_5) in which R_4 represents hydroxy or

esterified hydroxy which is cleavable under physiological conditions, and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen and R_6 represents a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl or in which X is oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl; and salts and metal ion complexes thereof.

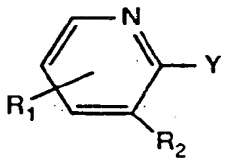
Especially preferred are compounds of the formula I in which R_1 represents hydrogen, R_2 represents hydroxy, and R_3 together with the carbonyl group to which it is attached, represents esterified carboxy which is cleavable under physiological conditions, and pharmaceutically acceptable salts thereof.

Especially preferred are likewise compounds of the formula I in which R_1 represents hydrogen, R_2 represents hydroxy, and R_3 represents a group of the partial formula -N(R_4,R_5) in which R_4 represents hydroxy and R_5 represents C_1-C_4 alkyl, and pharmaceutically acceptable salts thereof.

The invention relates especially to the compounds of the formula (I) mentioned in the examples, and to salts, especially pharmaceutically acceptable salts, thereof.

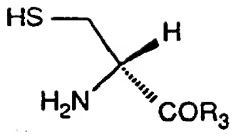
The compounds of the formula (I) according to the invention and salts thereof can be manufactured by chemical synthesis according to processes known per se. They are manufactured, for example,

a) by reacting a picolinic acid derivative of the formula (II)



(II)

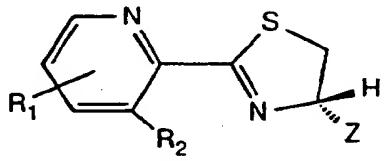
in which R_1 represents hydrogen, halogen, hydroxy, protected hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy, esterified or protected hydroxy and Y represents carboxy or a reactive functional derivative of a carboxy group, with a cysteine derivative of the formula (III)



(III)

in which R_3 represents etherified hydroxy or a group of the partial formula -N(R_4,R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl or in which R_4 represents hydroxy, esterified or protected hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl and the hydroxy group is optionally protected, or with a reactive functional derivative of said cysteine derivative (III), or,

b) in a compound of the formula (IV)



(IV)

in which R_1 and R_2 have the above meanings, by converting the radical Z which is a carboxy group or a reactive functional derivative thereof, into a group of the partial formula -COR_3 in which R_3 has the above meanings, and, if required, splitting off optionally present protecting groups, and/or, if desired, in a resulting compound of the formula (I) in which R_1 and/or R_2 and/or R_4 represent hydroxy, converting said hydroxy into esterified hydroxy, and/or, if desired, converting an obtainable compound of the formula (I) in which R_3 represents etherified hydroxy into a compound of the formula (I) in which R_3 represents a group of the partial formula -N(R_4,R_5), and/or converting an obtainable free compound of the formula (I) into a salt thereof.

The process is preferably carried out with optically pure (S) conformers of the compounds of the formula (III) and (IV).

Alkali and alkaline earth metal salts of 2-(3'hydroxypyrid-2'-yl)-2-thiazoline--4(S)-carboxylic acid and especially the sodium salt are novel compounds and can be prepared starting from the acid according to processes known per se, for example by reacting D-cysteine with 3-hydroxy-2-picolinonitrile and neutralization of the resulting optically pure acid with the corresponding anorganic base. These salts, especially the optically pure (S) contormers are valuable starting material for the production of the compounds of the formula (I) and exhibit valuable therapeutical properties.

Free hydroxy groups present in the compounds of the formula (II), (III) and (IV) are optionally protected by conventional protecting groups. Such protecting groups protect the hydroxy groups from undesired condensation reactions, substitution reactions and the like. The protecting groups can be introduced and removed readily, i.e. without undesirable secondary reactions taking place, for example by solvolysis or reduction, in a manner known per se. Protecting groups and the methods by which they are introduced and split off are described, for example in "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973, and also in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, vol. 15/1, Georg Thieme Verlag, Stuttgart 1974.

Suitable hydroxy-protecting groups are, for example, acyl radicals, such as lower alkanoyl optionally substituted, for example by halogen, such as 2,2-dichloroacetyl, or acyl radicals of carbonic acid semiesters, especially tert.-butoxycarbonyl, optionally substituted benzyl-oxycarbonyl, for example 4-nitrobenzyloxycarbonyl, or diphenylmethoxycarbonyl, alkenyloxycarbonyl, for example allyloxycarbonyl, or 2-halo-lower alkoxycarbonyl, such as 2,2,2-trichloroethoxycarbonyl, also trityl or formyl, or organic silyl radicals, also etherifying groups that can readily be split off, such as tert.-lower alkyl, for example tert.-butyl, or 2-oxa- or 2-thia-cycloalkyl having 5 or 6 ring atoms, for example tetrahydrofuryl or 2-tetrahydropyranyl or corresponding thia analogues, and also optionally substituted 1-phenyl-lower alkyl, such as optionally substituted benzyl or diphenylmethyl, there coming into consideration as substituents of the phenyl radicals, for example, halogen, such as chlorine, lower alkoxy, such as methoxy, and/or nitro.

A reactive functional derivative of a carboxy group (Y or Z in the compounds of the formula (II) or (IV)) is, for example, an acid anhydride, an activated ester or an activated amide, furthermore, as radical Y, also cyano, a group of the formula $-C(OR_a)_3$ or $-C(=NH)-R_a$ in which R_a is lower alkyl. Corresponding derivatives are well-known in the art.

Of the anhydrides, the mixed anhydrides are especially suitable. Mixed anhydrides are, for example, those with inorganic acids, such as hydrohalic acids, i.e. the corresponding acid halides, for example chlorides or bromides, also with hydrazoic acid, i.e. the corresponding acid azides. Further mixed anhydrides are, for example, those with organic carboxylic acids, such as with lower alkanecarboxylic acids optionally substituted, for example by halogen, such as fluorine or chlorine, for example pivalic acid or

trichloroacetic acid, or with semiesters, especially lower alkyl semiesters of carbonic acid, such as the ethyl or isobutyl semiester of carbonic acid, or with organic, especially aliphatic or aromatic, sulphonic acids, for example p-toluenesulfonic acid. Of the activated esters, there may be mentioned, for example: esters with vinylogous alcohols (i.e. enols, such as vinylogous lower alkenols), or iminomethyl ester halides, such as dimethylimino-methyl ester chloride (prepared from the carboxylic acid and, for example, dimethyl-(1-chloroethylidene)-iminium chloride of the formula $(CH_3)_2N^{\oplus}=C(Cl)CH_3Cl^{\ominus}$, which can be obtained, for example, from N,N-dimethylacetamide and phosgene), or aryl esters, such as preferably suitable substituted phenyl esters, for example phenyl esters substituted by halogen, such as chlorine, and/or by nitro, for example 4-nitrophenyl ester, 2,3-dinitrophenyl ester or 2,3,4,5,6-pentachlorophenyl ester, N-hetero-aromatic esters, such as N-benztriazole esters, for example 1-benztriazole ester, or N-diacylimino esters, such as N-succinylimino or N-phthalylimino ester. Suitable activated amides are, for example, imidazolides, also 1,2,4-triazolides, tetrazolides or 1,2,4-oxadiazolinonides.

The activation of a carboxy group Y or Z in the compounds of the formula II or IV can also be effected in situ.

A reactive functional derivative of a cysteine of the formula (III) is a compound in which the amino and/or mercapto group is activated for the reaction with the carboxy group of a compound of the formula (II), that is to say is present in nucleophilic form. The amino group is activated, for example, by reaction with a phosphite.

The reaction of the compound of the formula (II) in which Y represents carboxy with the cysteine derivative of the formula (III) according to process a) is preferably carried out in the presence of a suitable condensation agent or under dehydrating conditions, for example while removing the water of reaction by azeotropic distillation. Customary condensation agents are, for example carbodiimides, for example N,N'-diethyl-, N,N'-dipropyl-, N,N'-dicyclohexyl- or N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide, suitable carbonyl compounds, for example carbonyldiimidazole, or 1,2-oxazolium compounds, for example 2-ethyl-5-phenyl-1,2-oxazolium 3'-sulphonate or 2-tert.-butyl-5-methyl-isoxazolium perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, furthermore diphenylphosphoryl azide. The condensation reaction is carried out preferably in an anhydrous reaction medium, preferably in the presence of a solvent or diluent, for example methylene chloride, benzene or tetrahydrofuran and, if necessary, while cooling or heating, for example at

ambient temperature or at slightly elevated temperature, and/or in an inert gas atmosphere. If a compound of the formula (II) in which Y represents an acid anhydride derivative of a carboxy group is applied the reaction is performed under essentially the same conditions in the presence of a basic agent such as the sodium or potassium salt of carbonic acid, or a tertiary amino compound such as a tri-C_1-C_4-alkyl amine, for example triethylamine, or a pyridine base such as pyridine or quinoline.

A preferred form of process a) according to the invention is the reaction of a compound of the formula (II) in which Y represents cyano with a cysteine derivative of the formula (III). The reaction is carried out in an inert solvent such as an aqueous solvent at ambient temperature or, preferably, at slightly elevated temperature, for example at about 50° to 80°C, and preferably under an inert gas atmosphere

A preferred form of process b) according to the invention is the reaction of a compound of the formula (IV) in which Z represents carboxy or a reactive functional derivative thereof, for example an activated ester, with an alkanol of the formula R_3'-OH or with a compound which is convertible into an alkanol of the formula R_3'-OH (R_3'O corresponds to etherified hydroxy R_3 in the resulting compound of the formula (I)), for example a corresponding ketal of a di-C_1-C_2-alkyl keton such as acetone, for the preparation of a methyl ester especially 2,2-dimethoxy- or diethoxy-propane, or with an amine of the formula HN(R_4,R_5). In the alternative, for the synthesis of a compound of the formula (I) in which R_3 is an etherified hydroxy group, Z in a starting compound of the formula (IV) may also be a carboxy group in the salt form, such as the group -COOMe in which Me is, for example, a univalent cation of an alkali metal such as Na^+ or K^+. Such salt is reacted with a compound of the formula R_3'-Z' in which R_3' has the above meaning and Z' represents a reactive functional derivative of a hydroxy group. A reactive functional derivative of a hydroxy group is, for example, an ester with an inorganic acid, such as hydrohalic acid, i.e. the corresponding halide, for example chloride or bromide, or with an organic, especially aliphatic or aromatic, sulfonic acids, for example methanesulfonic acid, p-toluenesulfonic acid or m-bromobenzenesulfonic acid. It is also possible to use diazo-C_1-C_4-alkanes, especially diazomethane, which upon reaction with a compound of the formula (IV) in which Z represents carboxy yields the corresponding C_1-C_4-alkyl ester.

For example, for the preparation of a compound of the formula (I) in which R_3 represents etherified hydroxy according to process b) a carboxylic acid compound of the formula

(IV) (Z represents carboxy) is reacted with an alcohol of the formula R_3'-OH in an inert solvent in the presence of a condensation agent such as a carbodiimide or an acidic agent such as an aromatic sulfonic acid as defined above while heating or the reaction is done with the formed water being removed from the reaction mixture by azeotropic distillation. In the alternative it is also possible to react in an inert solvent while cooling, for example at about 0°C, a carboxylic acid compound of the formula (IV) (Z represents carboxy) with a diazo-C_1-C_4-alkane, especially diazomethane, to obtain a compound of the formula (I) in which R_3 represents C_1-C_4 alkoxy, especially methoxy.

For the preparation of a compound of the formula (I) in which R_3 represents a group of the formula -N(R_4,R_5), for example, a compound of the formula (IV) in which Z is a reactive functional derivative of a carboxy group, is reacted with an amine of the formula HN(R_4,R_5). A preferred functional derivative of a carboxy group according to the invention is the N-succinylimino ester. The reaction is performed in an inert solvent such as an aprotic solvent for example dimethylformamide, dimethylsulfoxide or dioxane or an C_1-C_4 alkanol such as methanol, at ambient temperature or while cooling, for example at about 0°C.

In a resulting compound of the formula (I) in which one or more functional (hydroxy) groups are protected, the latter can be freed, optionally in stages or simultaneously, in a manner known per se, by means of solvolysis, especially hydrolysis or acidolysis, or in some cases also by means of careful reduction. Silyl protecting groups are advantageously split off with fluorides, for example tetraethylammonium fluoride.

The compounds of the formula (I) obtainable according to the invention can be converted in a manner known per se into other compounds of the formula (I).

For example, in a compound of the formula (I) in which R_2 and/or R_4 represent hydroxy the hydroxy group(s) can be converted into (a) esterified hydroxy group(s). The conversion can be performed, for example, by reacting a salt of a compound of the formula (I), for example the sodium salt or disodium salt, of the phenolic hydroxy group R_2 and/or of the hydroxylamine hydroxy group R_4 with an acylating agent of the formula Ac_1-Z' in which Ac_1 is the acylating group which together with the hydroxy oxygen atom forms the esterified hydroxy group R_2 and/or R_4, and Z' represents a reactive functional derivative of a hydroxy group as defined above.

Furthermore, an obtainable compound of the formula (I) in which R_3 represents etherified hydroxy can be converted into a compound of the formula (I) in which R_3 represents a group of the partial formula $-N(R_4,R_5)$. The reaction is performed essentially as described under process b) using a compound of the formula (I) in which R_3 represents etherified hydroxy as starting material in place of a corresponding compound of the formula (IV) in which Z is a reactive functional derivative of a carboxy group, and reacting it with an amine of the formula $HN(R_4,R_5)$.

Salts of compounds of the formula (I) can be manufactured in a manner known per se. Thus, salts of compounds of the formula (I) having acidic groups (for example R_4 represents hydroxy) can be formed, for example, by treating with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, for example the sodium salt of α-ethylcaproic acid, or with inorganic alkali metal or alkaline earth metal salts, for example sodium bicarbonate, or with ammonia or a suitable organic amine, preferably stoichiometric quantities or only a small excess of the salt-forming agent being used. Acid addition salts of compounds of the formula (I) are obtained in customary manner, for example by treating with an acid or a suitable anion-exchange reagent. Internal salts of compounds of the formula (I) (zwitterionic forms) can be formed, for example, by neutralising the compounds or salts, such as acid addtion salts, to the isoelectric point, for example with weak bases, or by treating with liquid ion-exchangers.

Salts can be converted in customary manner into the free compounds: metal and ammonium salts can be converted into the free compounds, for example, by treating with suitable acids, and acid addition salts, for example, by treating with a suitable basic agent.

The starting materials, especially those of formula (II) and (III) as well as amines of the formula $HN(R_4,R_5)$, are available commercially and/or known or can be manufactured by known processes. Starting compounds of the formula (IV) in their racemic form are known from U.S. Patent No. 4,406,905 or can be prepared in an analogous manner as described therein. The racemates can be split in a manner known per se, for example after conversation of the optical antipodes into diastereoisomeres, for example by reaction with optically active acids or bases. Hydroxylamine compounds of the formula $HN(R_4,R_5)$ in which R_4 represents optionally esterified or protected hydroxy and R_5 represents a group of the partial formula $-X-R_6$ as defined above can be manufactured in a manner known per se. For example, a hydroxylamine compound of the formula $HN(R_4,R_5)$ in which R_4 represents hydroxy and R_5 represents a group $-X-N(OH)-R_7$ as defined above can be

manufactured in the following manner:

A diprotected hydroxylamine such as N-BOC-O-benzyl hydroxylamine (compound A) is alkylated with a ω,ω'-dichloro-C_2-C_{12}-alkane in the presence of a strong base such as sodium hydride; in the resulting N-(ω-chloro-C_2-C_{12}-alkyl)-N-BOC-O-benzyl hydroxylamine the BOC protecting group is removed by treatment with trifluoroacetic acid in methylene chloride and the resulting deprotected compound is reacted with a C_1-C_4-alkanoyl (R_7 residue) chloride in the presence of a basic agent such as sodium hydroxide (for example in a mixed solvent water/methylene chloride) to yield the corresponding N-(C_1-C_4-alkanoyl)-N-(ω-chloro-C_2-C_{12}-alkyl)-O-benzyl hydroxylamine (compound B); the above compound A is reacted with compound B in the presence of a strong basic agent such as sodium hydride and after reductive (H_2 in, for example methanol) removal of the hydroxy protecting groups (benzyl) N-(C_1-C_4-alkanoyl)-N-[ω-(N-BOC-N-hydroxy-amino)-C_2-C_{12}-alkyl]-hydoxylamine (compound C) is obtained. Compound C is treated with trifluoroacetic acid in methylene chloride in order to remove the BOC protecting group resulting in the desired starting compound N-(C_1-C_4-alkanoyl)-N-[ω-(N-hydroxy-amino)-C_2-C_{12}-alkyl]-hydoxylamine [HN(R_4,R_5) in which R_4 represents hydroxy and R_5 represents a group -X-N(OH)-R_7 in which X is C_2-C_{12}-alkylen and R_7 is C_1-C_4-alkanoyl].

The pharmacologically acceptable compounds of the present invention can be used, for example, for the manufacture of pharmaceutical compositions which contain an effective amount of the active substance together or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

The pharmaceutical compositions according to the invention are those which are suitable for enteral, such as oral, administration and for parenteral, such as subcutaneous, administration to warm-blooded animals, especially humans, and which contain the pharmacological active substance on its own or together with a pharmaceutically acceptable carrier. The dosage of the active substance depends on the species of warm-blooded animal and on the age and individual condition, the illness to be treated and also on the mode of administration.

The novel pharmaceutical proparations contain from approximately 10 % to approximately 95 %, preferably from approximately 20 % to approximately 90 %, of the active substance. Pharmaceutical compositions according to the invention can, for

example, be in unit dose form, such as dragées, tablets, capsules, suppositories or ampoules, and contain from approximately 0.1 g to approximately 3.0 g, preferably from approximately 0.3 g to approximately 1.0 g, of the active ingredient.

The pharmaceutical compositions of the present invention are manufactured in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. Pharmaceutical compositions for oral use can be obtained by combining the active substance with one or more solid carriers, if desired granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, to form tablets or dragée cores. In so doing, they can also be incorporated into plastics carriers which release the active substances or allow them to diffuse in controlled amounts.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders such as starches, for example corn, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinyl-pyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating and lubricating agents, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings that are, if desired, resistant to gastric juice, there being used, inter alia, concentrated sugar solutions which optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures or, for the manufacture of coatings that are resistant to gastric juice, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropyl-methylcellulose phthalate. Colouring substances or pigments can be added to the tablets or dragée coatings, for example for the purpose of identification or for indicating different doses of active substance.

Other orally administrable pharmaceutical compositions are dry-filled capsules made of gelatin, and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as corn starch, binders and/or

glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids or wax-like substances, such as fatty oils, paraffin oil or polyethylene glycols, it being possible also for stabilisers to be added.

Other forms of oral administration are, for example, syrups prepared in customary manner that contain the active ingredient in, for example, suspended form and in a concentration of approximately from 5 % to 20 %, preferably approximately 10 %, or in a similar concentration that provides a suitable single dose when administered, for example, in measures of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for preparing shakes, for example in milk. Such concentrates can also be packed in single-dose quantities.

Particularly suitable dosage forms for parenteral administration are sterile aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, or sterile aqueous injection suspensions which contain substances increasing the viscosity, for example sodium carboxymethyl cellulose, sorbitol and/or dextran, and optionally stabilisers. In addition, the active ingredient, with or without adjuvants, can also be in lyophilised form and brought into solution prior to parenteral administration by addition of suitable solvents.

The invention relates also to compositions for diagnostic purposes that contain a suitable metal complex of a compound of the formula (I) in which R_1 has the above meanings, R_2 represents hydroxy and R_3 represents a group of the formula $-N(R_4,R_5)$ in which R_4 represents hydroxy and R_5 has the above meanings, preferably in the form of an aqueous solution or in the form of a dry preparation.

The invention relates also to a method of treatment of pathological conditions in a mammal, especially human, which, as has been described hereinbefore, are associated with an excess of a trivalent metal cation such as aluminium or, especially, iron(III), in the body, which method comprises administering, preferably orally, a prophylactically or therapeutically effective amount of a compound of formula (I) or of a pharmaceutically acceptable salt thereof. There are used for this purpose especially the above-mentioned pharmaceutical compositions, a daily dose of from approximately 100 mg to approximately 2000 mg, preferably from approximately 300 mg to approximately 1000 mg, of a compound of the present invention being administered to a warm-blooded animal

of approximately 70 kg body weight. The dosage can be administered orally in several, for example three, individual doses. For systemic, e.g. subcutaneous, administration the more water soluble salt forms of the compounds of the formula (I), e.g. the sodium salt, are preferred. for example orally, or alternatively subcutaneously.

The invention concerns especially the compounds of the formula (I), the methods for the preparation thereof and pharmaceutical compositions as described in the examples.

The following examples serve to illustrate the invention but should not be construed as a limitation thereof. Temperatures are given in degrees Centigrade.

Example 1: 2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylic acid
(optically pure, zwitterionic form)

A mixture of 30 ml each of 1 M phosphate buffers of pH 7.0 and 4.5 respectively is placed in a reaction flask and diluted with 350 ml of methanol and 250 ml of water treated in a Nanopur water purification system. The diluted buffer solution is degassed by passing a vigorous stream of argon through the solution. After addition of 20.0 g (165 mmole) of D-cysteine the temperature of the solution is raised to 35° in a heating bath under continuous agitation. As soon as the D-cysteine is almost completely dissolved a quantity of 9.91 g (82.5 mmole) of 3-hydroxy-2-picolinonitrile is added in one portion. The pH of the reaction mixture is adjusted to a value of 7.5 by the addition of 2 N sodium hydroxide solution. The almost clear solution is subsequently heated to 65-70° and stirred under argon atmosphere in order to avoid formation of cystine by oxygen. The reaction is terminated after 8 hrs. The clear solution with the pH value of 8.2 is concentrated on a rotary evaporator under reduced pressure. 300 ml of methylene chloride are added to the aqueous concentrate. The mixture is acidified to pH 2.5 by addition of 4N hydrochloric acid. The organic extract is separated and the aqueous phase is reextracted twice with small portions of methylene chloride. The combined organic extracts are washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness. The residue is recrystallized from methanol, yielding bright yellow needles with a m.p. of 144-46°. The crystallisate still contains traces of water (0.05 mol. equiv.) after drying in the high vacuum:
elemental analysis (for $C_9H_8N_2O_3S \cdot 0.05\ H_2O$)

% calc.:	C	48.01	% found:	C	48.00
	H	3.63		H	3.68
	N	12.44		N	12.41
	S	14.24		S	13.97

optical rotation (c = 1.42 % in dioxan): 436 nm = -44.3°/546 nm = -23.9° ± 0.7°/578 nm = -20.2° ± 0.7°/589 nm (Na_D) = 19.5° ± 0.7°

Example 2: Sodium 2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate

16.82 g (75 mmole) of the acid as prepared in example 1 is suspended in 400 ml of deionized water. The pH value is slowly raised by addition of 2 N sodium hydroxide under stirring. The pH of 7.0 is reached after addition of exactly one molar equivalent (37.5 ml). The clear solution is lyophilised to yield an amorphous yellow powder.

After drying under high vacuum the sodium salt contained one molar equivalent of water: elemental analysis (for $C_9H_6NaN_2O_3S \cdot H_2O$)

% calc.:	C	40.91	% found:	C	40.74
	H	3.43		H	3.40
	N	10.60		N	10.59
	Na	8.70		Na	8.90
	S	12.13		S	11.92

optical rotation (c = 0.261 % in DSMO): 546 nm = -124.5°/578 nm = -101.5°/589 nm (Na_D) = 94.6° ± 3.8°

UV spectrum in ethanol: $\lambda_{max}(\epsilon)$ = 311 nm (9800), sh at 240 nm

Example 3: Pivaloyloxymethyl-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate

3.36 g (15 mmole) of sodium 2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate as prepared in example 2 is suspended in 150 ml of methylene chloride. After addition of 2.1 ml (15 mmole) of triethylamine and 3.60 ml (16.5 mmole) of iodomethylpivalate with a purity of 79 % the reaction mixture is stirred at room temperature. After 2 hrs. an

additional amount of 1 ml of the iodomethylpivalate is added to the suspension. Stirring is continued during further 20 hrs. at room temperature. The reaction mixture is extracted with two 100 ml portions of phosphate buffer of pH 7.0 and an equal amount of sodium thiosulfate solution. The organic phase is evaporated to dryness. The residue (7.25 g) is redissolved in methanol. The dark colored solution is treated with charcoal. The solvent is evaporated and the oily residue is taken up in diethyl ether. A small precipitate of starting material (0.4 g) is removed by filtration. The oily residue (6.54 g) obtained after evaporation of the solvent is redissolved in a small amount of methylene chloride and transferred on a chromatographic column containing 160 g of silicagel. The pure ester is eluted with 400 ml of methylene chloride containing 10 % of methanol. The fractions containing the pure product are combined and concentrated in vacuo yielding the desired product in the form of a yellow oil.

IR - spectrum in methylene chloride : main absorption bands at 1758 (very strong band), 1592, 1451, 1302, 1183, 1110 and 991 cm^{-1}.

UV-spectrum : $\lambda_{max.}(\epsilon)$ = 311 nm (9180), 202 nm (26'400) sh at 239 nm
$\lambda_{min.}$ = 256 nm (1'015)

optical rotation (c = 2.59 % in ethanol) : 546 nm = -4,5° ± 0.4 %/578 nm = -4.2° ± 0.4 %/589 nm = -3.6° ± 0.4%

Example 4: Succinimido -2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate

112.1 mg (0.5 mmole) of 2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylic acid and 65.3 mg (0.55 mmole) N-hydroxysuccinimide are placed in a 3-neck reaction vessel and purged with nitrogen gas. The reactants are dissolved in 6 ml of dry tetrahydrofurane and cooled to 0° in an ice-bath. Under stirring a solution of 113.5 mg (0.55 mmole) of N, N'-dicyclohexyl-carbodiimide in 4 ml of dry tetrahydrofurane is slowly added and stirring continued for 30 min. at 0°. The resulting suspension is kept at room temperature overnight. The solid precipitate of N,N'-dicyclohexyl-urea is filtered off and washed with 15 ml of ethyl acetate. The solvents are evaporated on a rotatory evaporator and the resulting solid is recrystallized from ethyl acetate. Two crops of crystals are collected and washed with ice-cold solvent. The pooled crystallizate is dried in the high vacuum.

^{1}H-NMR ($CDCl_3$+DMSO-d_6-TMS): 8.15 (t, 1H), 7.30 (d, 2H), 5.73 (t, 1H), 3.72 (d, 2H),

2.83 ppm (s. 4H)

elemental analysis (for $C_{13}H_{12}N_2O_5S$)

% calc.:	C	48.60%	% found:	C	48.55
	H	3.45		H	3.50
	N	13.08		N	12.97

Example 5: N-methyl-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4-hydroxamic acid
(Racemic mixture)

1.0 g (3.11 mmole) of the N-hydroxysuccinimidoester prepared in the previous example is placed in a 3-neck reaction flask and dissolved in 20 ml dry degassed dimethylformamide. Under cooling to 0° a clear solution of N-methyl-hydroxylamine in DMF is dropped and stirring continued at 0° during 3.5 hr. The latter solution is prepared before from 2.6 g (31.1 mmole) of N-methyl hydroxylamine hydrochloride in 20 ml of abs. dimethyl-formamide by slow addition of a solution of 3.15 g (31.1 mmole) of triethylamine in 5 ml of dimethylformamide at 0°, stirring for 30 min. and filtration of the triethylamine hydrochloride.

After completion of the reaction the solvent is evaporated under vacuum. The resulting oil is triturated with 30 ml of an aqueous saturated solution of sodium bicarbonate at 0° to get a precipitate. The mixture is extracted repeatedly with 40 ml of chloroform and the solvent is removed to give a solid crude product which is almost homogenous by thin-layer chromatography on silicagel plates developed with chloroform containing 6 % of ethanol as the solvent system.

The crude product is further purified by chromatography on 20 g of Sephadex LH-20 resin. The solid material is first dissolved in a small amount of methanol. To the concentrated solution 1.5 g of Sephadex LH-20 is added and the suspension is dried under vacuum overnight. The dried residue is applied on top of the column and elution is performed with toluene/ethanol in the ratio of 19:1. Elution of the product is monitored by chromatography on silicagel thin-layer plates. The fractions containing pure material are pooled, evaporated to dryness and recrystallized from toluene/ethanol to yield colorless needles, m.p. 158-159°.

^{1}H-NMR (DMSO-d_6-TMS): 8.15 (t, 1H), 7.42 (d, 2H), 5.90 (t, 1H), 5.90 (t, 1H), 3.53 (d, 1H), 3.47 (d, 1H), 3.27 ppm (s, 3H)

elemental analysis (for $C_{10}H_{11}N_3O_3S$)

% calc.:	C	47.20	% found:	C	47.52
	H	4.38		H	4.40
	S	16.59		S	16.65

To isolate the optically pure (S) conformer either the racemate can be split in a manner known per se, for example after conversation of the optical antipodes into diastereo-isomeres, for example by reaction with optically active acids or bases or the optically pure form can be prepared as described below in detail.

Example 6: N-methyl-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S) hydroxamic acid (optically pure, zwitterionic form)

224.2 mg (1.0 mmole) 2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylic acid and 83.5Amg (1.0 mmole) N-methyl-hydroxylamine hydrochloride are placed in a 3-neck reaction vessel and purged with nitrogen gas. The reactants are dissolved in 6 ml degassed dimethylformamide (DMF). After cooling to 0°C in an ice-bath 442.3 mg (1 mmole) of BOP-reagent [benzotriazole-1-yloxy tris(dimethylamino)phoshonium hexafluorophosphate] is added. Under stirring a solution of 129.3 mg (1.0 mmole) diisopropylethylenediamine in 4 ml DMF is slowly dripped into the above solution at 0°C. After continued stirring for 20 minutes at 0°C and overnight at room temperature the solvent is evaporated under high vacuum. The resulting residue is redissolved in 30 ml ethyl acetate and washed successively with 10 ml saturated sodium bicarbonate solution, 10 ml saturated sodium chloride, 10 ml 10 % aq. citric acid solution and again with 10 ml saturated sodium chloride solution. The organic phase is dried over anhydrous sodium sulfate, filtered and evaporated to dryness on a rotatory evaporator. The crude product is purified by column chromatography on Sephadex LH 20 using a solution of 3 % of ethanol in toluene as the eluent. The fractions containing the pure desired compound are combined and evaporated to dryness leaving 120 mg (47 % yield) of a chromatographically homogeneous yellow solid.

^{1}H-NMR ($CDCl_3$ and DMSO-d_6-TMS): δ 8.15 (t,1H); 7.30 (d,2H); 5.70 (t,1H); 3.53 (dd,A2H); 3.27 (s, 3H).

elemental analysis (for $C_{10}H_{11}N_3O_3S$)

% calc.:			% found:		
	C	47.42		C	47.66
	H	4.38		H	4.41
	N	16.59		N	16.45

optical rotation (c = 2.335 % in methanol):
589 nm (Na_D) = -41.3°

Example 7: Magnesium bis [2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate]

11.2 g (46.23 mmole) of the acid in the form of the monohydrate is suspended in 400 ml of deionized water. Magnesium hydroxide (FLUKA, > 95 %) is added in portions under pH control over a period of 2 hr. The pH value is increased from 3.0 to 5.0 after addition of a total of 1.53 g of the magnesium hydroxide (25 mmole of > 95 % pure reagent). The clear solution is lyophilized yielding 10.7 g (98.4 %) of the desired product.

elemental analysis (for $C_{18}H_{14}MgN_4O_6S_2 \cdot 2.75$ mole of H_2O)

% calc.:			% found:		
	C	41.55		C	41.75
	H	3.78		H	3.64
	Mg	4.67		Mg	4.63
	N	10.77		N	10.77
	S	12.32		S	12.18

optical rotation (c = 0.885 % in H_20):
546 nm = +108.5°/578 nm =
+89.5°/589 nm (Na_D) = +84.4° ± 1.1°

Example 8: 2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4-hydroxamic acid
(Racemic mixture)

126.35 mg (1.8 mmole) hydroxylamine hydrochloride is placed in a 3-neck reaction vessel purged with dry nitrogen. The reagent is dissolved in 4 ml dry methanol under stirring for 5 min. at 0°. To the clear solution 1.8 ml 1 M sodium methoxide in dry methanol (1.8 mmole) is added slowly over a period of 5 min. and stirring is continued for 10 min. at 0°. The resulting suspension is added dropwise to a slurry prepared from 357.6 mg (1.5 mmole) of methyl-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate in 33 ml of dry methanol, which has been purged with nitrogen and cooled in an ice-bath. The empty glassware is washed with 2.2 ml of dry methanol. After completion of the addition the reaction mixture is stirred during 30 min. and subsequently allowed to warm up to room temperature. The turbid solution clears up and stirring is continued for one hour at room temperature. Examination by thin-layer chromatography on silicagel (solvent system chloroform/methanol 9:1) reveals only traces of the starting material. The solvent is removed in a rotatory evaporator and the yellow residue is triturated with benzene. The crude product is purified by preparative chromatography on a column containing 20 g of silicagel. The desired product is eluted with a mixture of chloroform/methanol (9:1). Fractions containing the pure product are pooled and evaporated to dryness, yielding a light yellow solid.

m.p. 163-165°

^{1}H-NMR (DMSO-d_6): 8.15 (t, 1H), 7.43 (d, 2H), 5.27 (t, 1H), 3.52 ppm (d, 2H)

elemental analysis (for $C_{13}H_{11}N_3O_5S$)

% calc. :	C	48.60	% found :	C	48.55
	H	3.45		H	3.50
	N	13.08		N	12.97

To isolate the optically pure (S) conformer either the racemate can be split in a manner known per se, for example after conversation of the optical antipodes into diastereo-isomeres, for example by reaction with optically active acids or bases or the optically pure form can be prepared as described below in detail.

Example 9: N-[5-(N-acetyl-N-hydroxy-amino)-pentyl]-2-(3'-hydroxypyrid-2'-yl)-Δ^2--thiazoline-4(S)-hydroxamic acid

(a) N-(tert-Butoxycarbonyl)-O-benzylhydroxylamine (4 g, 18 mmol) is dissolved in DMF (60 ml). NaH (80 %, 0,591 g, 19,7 mmol) is added in portions at 0°, and followed by stirring at 0° for 30 min. A solution of 1,5-dichloropentane (12.8 g, 89.6 mmol) in DMF (20 ml) is slowly dripped in, and the solution is stirred at 0° for 20 min. and 70-80° overnight. The solvent is removed under high vacuum, and the residue is quenched with water (50 ml) at 0°. The aqueous layer is extracted with CH_2Cl_2 (4 x 40 ml), and the organic fractions are combined and dried over Na_2SO_4. Drying agent is filtered, and the solvent is removed. The crude oil is purified by silica gel column chromatography using 1:29:70 EtOAc:$CHCl_3$:hexanes as eluant, to give N-(5-chloropentyl)-N-(tert-butoxycarbonyl)-O-benzylhydroxylamine as an oil.

^{1}H-NMR ($CDCl_3$): δ 1.47 (s, 9 H), 1.30-1.90 (m, 6 H), 3.40 (t,2 H), 3.47 (t, 2 H), 4.80 (s, 2 H), 7.30 (s, 5 H). Anal. calcd. for $C_{17}H_{26}ClNO_3$ (%): C 62.28; H 7.99; N 4.27. Found: C 62.39; H 7.97; N 4.32.

(b) Trifluoroacetic acid (10 ml) is slowly dripped into a solution of N-(5-chloropentyl)-N-(tert-butoxycarbonyl)-O-benzylhydroxylamine (3.00 g, 9.15 mmol) in CH_2Cl_2 (100 ml), which has been cooled to 0°. The reactants are stirred at 0° for 20 min and RT for 15 min. The volatiles are removed on a rotary evaporator, satured $NaHCO_3$ (60 ml) is added and product extracted with CH_2Cl_2 (4 x 50 ml). Combined organic extracts are dried over Na_2SO_4, filtered, and the solvent is removed. The resulting oil is passed through a short silica gel column, eluting with CH_2Cl_2, providing N-(5-chloropentyl)-O-benzylhydroxylamine as an oil.

^{1}H-NMR ($CDCl_3$): δ 1.33-1.90 (m, 6 H), 2.87 (t,2 H), 3.43 (t, 2 H), 4.30 (br s, 1 H), 4.60 (s, 2 H), 7.18 (s, 5 H). Anal. calcd. for $C_{12}H_{18}ClNO$ (%): C 63.29; H 7.97; N 6.15. Found: C 63.38; H 8.03; N 6.13.

(c) 1 N NaOH (25 ml) is added to a solution of N-(5-chloropentyl)-O-benzylhydroxylamine (2.13 g, 9.35 mmol) in CH_2Cl_2 (35 ml), which has been cooled to 0°. Acetyl chloride (1.123 g, 14.02 mmol) in CH_2Cl_2 (15 ml) is added dropwise at 0° to the biphasic mixture, which is efficiently stirred for 20 min at 0° and overnight at RT. The layers are

separated, and the aqueous phase is further extracted with CH_2Cl_2 (3 x 50 ml). The combined organic fractions are washed with brine (100 ml), dried over Na_2SO_4, and concentrated. Purification on silica gel chromatography using 80 % hexanes/EtOAc as an eluant produces N-acetyl-N-(5-chloropentyl)-O-benzylhydroxylamine as an oil.

^{1}H-NMR ($CDCl_3$): δ 1.33-1.90 (m, 6 H), 2.07 (s, 3 H), 3.48 (t,2 H), 3.60 (t, 2 H), 4.80 (s, 2 H), 7.33 (s, 5 H). Anal. calcd. for $C_{14}H_{20}ClNO_2$ (%): C 62.33; H 7.47; N 5.19. Found: C 62.12; H 7.43; N 5.11.

(d) NaH (80 %, 0.323 g, 10,8 mmol) is added in portions to a solution of N-(tert-butoxy-carbonyl)-O-benzylhydroxylamine (2.19 g, 9,79 mmol) in DMF (45 ml) at 0°. The mixture is stirred at 0° for 20 min, followed by cautious addition of a solution of N-acetyl-N-(5-chloropentyl)-O-benzylhydroxylamine (2.4 g, 8.9 mmol) in DMF (15 ml). Crude product is purified by silica gel column chromatography using 6:2:1 hexanes/EtOAc/$CHCl_3$ as eluant, to generate N-acetyl-N-[5-(N-BOC-N-benzyloxyamino)-pentyl]-O-benzyl-hydroxylamine as an oil.

^{1}H-NMR ($CDCl_3$): δ 1.23-1.80 (m, 6 H), 1,47 (s, 9 H), 2.03 (s, 3 H), 3.36 (t, 2 H), 3.57 (t, 2 H), 4.76 (s, 2 H), 4.78 (s, 2 H), 7.30 (s, 5 H). Anal. calcd. for $C_{26}H_{36}N_2O_5$ (%): C 68.40; H 7.95; N 6.14. Found: C 68.20; H 7.94; N 6.10.

(e) 10 % Pd-C (0.2 g) is added under nitrogen to a solution of N-acetyl-N-[5-(N-BOC-N-benzyloxyamino)-pentyl]-O-benzylhydroxylamine (1.020 g), 2.234 mmol) in distilled CH_3OH (80 ml). Hydrogenation is carried out at 1 atm for 2 h. Catalyst is filtred off and washed with CH_3OH. Solvent is removed, and the crude oil is purified by Sephadex LH-20 column chromatography using 4 % EtOH/toluene as an eluant, to give N-acetyl-N-[5-(N-BOC-N-hydroxyamino)-pentyl]-hydroxylamine as an oil.

^{1}H-NMR (CD_3OD): δ 1.20-1.83 (m, 6 H), 1,46 (s, 9 H), 2.07 (s, 3 H), 3.35-3.70 (m, 4 H). Anal. calcd. for $C_{12}H_{24}N_2O_5$ (%): C 52.16; H 8.75; N 10.14. Found: C 52.07; H 8.72; N 10.05.

(f) Trifluoroacetic acid (6 ml) is slowly dripped into a solution of N-acetyl-N-[5-(N-BOC-N-hydroxyamino)-pentyl]-hydroxylamine (540 mg, 1.95 mmol) in CH_2Cl_2 (20 ml) at 0°. Reactants are stirred at 0° for 20 min and RT for 15 min. The volatiles are removed on a rotary evaporator, dry benzene is added and evaporated a few times, and the resulting

oil is dried in vacuo to provide N-acetyl-N-(5-hydroxyamino-pentyl)-hydroxylamine (as the trifluoroacetate) as an oil.

^{1}H-NMR (CD_3OD): δ 1.23-1.87 (m, 6 H), 2.07 (s, 9 H), 3.17 (t, 2 H), 3.60 (t, 2 H).

(g) The N-hydroxysuccinimide ester of example 4 (603.3 mg, 1.878 mmol) is added to a solution of N-acetyl-N-(5-hydroxyamino-pentyl)-hydroxylamine trifluoroacetate (492,4 mg, 1.878 mmol) in THF (40 ml) at 0°. Next a solution of triethylamine (412.6 mg, 4.078 mmol) in THF (20 ml) is slowly added, and the solution is stirred at RT for 6 h. Solvent is removed, and distilled water (30 ml) is added to the light yellow oil, followed by extraction with $CHCl_3$ (3 x 50 ml). Solvent removal, as usual, and purification an a Sephadex LH-20 column using 4 % EtOH/toluene as eluant gives N-[5-(N-acetyl-N-hydroxy-amino)-pentyl]-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-hydroxamic acid as a thick oil.

^{1}H-NMR (CD_3OD): δ 1.30-1.90 (m, 6 H), 2.05 (s, 3 H), 3.40-3.80 (m, 6 H), 5.93 (t, 1 H), 7.30 (d, 2 H), 8.05 (t, 1 H).

Example 10: Methyl 2-(3-'hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate

33.6 g (0.15mole) of 2-(3-'hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylic acid as prepared in example A1 is suspended in 1.2 l of methylene chloride. After addition of 184 ml (1.5 mole) of 2.2-dimethoxypropane ("acetone dimethylacetal", Fluka, purum) and of 34.2 g (0.18 mole) of p-toluenesulfonic acid monohydrate, (Merck, p.a.) the reaction mixture is stirred at room temperature during a period of 6 hr. The reaction mixture is extracted with three portions of 300 ml each of 1-molar phosphate buffer pH 7.0. The organic phase is dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. The residue is dissolved in 300 ml of diethyl ether and stored in the refrigerator before filtration. The slightly yellow colored crystals are filtered, washed with cold diethyl ether and dried *in vacuo* (yield: 32.76 g, 91,7A%; m.p. 55-56 °C):

elemental analysis (for $C_{10}H_{10}N_2O_3S \cdot 0.05\ H_2O$)

% calc.:	C	50.41	% found:	C	50.48
	H	4.23		H	4.28
	N	11.76		N	11.67
	S	13.46		S	13.34

optical rotation (c = 2.0 % in dioxane):
546 nm = -15.4°/578 nm = -13.3°/589 nm (Na_D) = -12.6°
IR and ^{1}H-NMR spectra are compatible with the proposed structure.

Example 11: Ethyl 2-(3-'hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate

A suspension of 33.6 g (0.15 mole) of the acid as prepared in example 1 in 1 l of methylene chloride is stirred with 28.5 g (0.15 mole) of p-toluenesulfonic acid monohydrate and 120 ml (7.2 mole) of triethyl orthoformiate (Merck, p. synth.) at 4 °C during a period of 72 hr. The reaction mixture is extracted as in the previous example 9. The solvent is removed in vacuo and the dried residue (37.8 g) is crystallized from a 1:1 mixture of diethyl ether and heptane. After filtration of a first crop of crystals (21.14 g, m.p. 42-43 °C) a second crop of 14.07 g of a product with a purity of >95 % is obtained by concentration of the mother liquors (total yield: 35.21 g, 93 %). A sample of the vacuum-dried first crop of crystals gives the following analytical results:
elemental analysis (for $C_{11}H_{12}N_2O_3S \cdot 0.05\ H_2O$)

% calc.:	C	52.37	% found:	C	52.39
	H	4.79		H	4.75
	N	11.10		N	11.03
	S	12.71		S	12.70

optical rotation (c = 2 % in dioxane):
436 nm = -54.1°/546 nm = -31.1 ±0.5° /578 nm = -27.0°/589 nm (Na_D) = -25.9 ±0.5°

Example 12: N-[5''-(N-hydroxy-N-acetyl)-pentyl]-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-hydroxamic acid

80.0 mg (0.404 mmole) 5-(N-hydroxy-N-acetyl)-pentylamine hydrochlorid and 90.58 mg (0.404 mmole) 2-(3'-hydroxypyrid-2'yl)-Δ^2-thiazoline-4(S) carbocylic acid are dissolved in 8 ml of degassed dimethylformamid (DMF). After cooling to 0°C 178.7 mg (0.404 mole) of benzotriazol-1-yloxy tris(dismethylamino)-phosphonium hexafluorophosphate is added to the solution. After slowly adding a solution of N,N'-diisopropylidendiamine in 2

ml DMF, the reaction mixture is stirred for 15 minutes at 0°C and over night at room temperature. The solvent is removed at reduced pressure (high vacuum) and the residue taken up in 40 ml of ethyl acetate. The organic phase is subsequently washed with 10 ml of saturated sodium bicarbonate solution, 10 ml of saturated saline, 10 ml of 10 % aqueous citric acid and again with 10 ml of saturated saline. The organic phase is dried over anhydrous sodium sulfate, filtered and evaporated to dryness in a rotatory evaporator. The oily residue is purified by column chromatography on Sephadex LH-20 using 4% ethanol in toluene as the eluent. The fractions giving a single spot on TLC are combined and evaporated to dryness, leaving 93 mg (60 %) of pure title compound as a yellow colored oil.

^{1}H-NMR (CD_3OD, δ TMS): 8.06 (t, 1H); 7.33 (d, 2H); 3.40 - 3.80 (m, 6H); 2.06 (s, 3H): 1.30 - 1.90 (m, 6H)

optical rotation (c = 9.85 % in methanol):
589 nm = (Na_D, 25°C) = 16.7°

Example 13: Pharmaceutical composition for oral administration

1000 gelatine capsules each containing 250 mg of active ingredient are manufactured as follows:

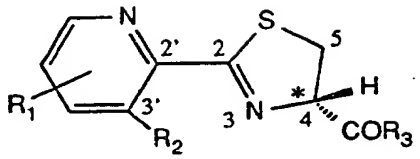
Composition:

250 g	N-methyl-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-hydroxamic acid
36 g	talc
24 g	wheat starch
16 g	magnesium stearate
4 g	lactose

The pulverulent substances are forced through a sieve having a mesh width of 0.6 mm and mixed thoroughly to yield a total of 330 g. 1000 gelatine capsules are each filled with 330 mg of this mixture using a capsule filling machine.

What we claim is:

1. A compound of the formula (I)



(I),

in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy or esterified hydroxy; and R_3 represents etherified hydroxy or a group of the partial formula -N(R_4,R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl or in which R_4 represents hydroxy or esterified hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl; and salts thereof.

2. A compound of the formula (I) according to claim 1 in which
(a) R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl;
R_2 represents hydroxy or esterified hydroxy; and
R_3 represents, together with the carbonyl group to which it is attached, an esterified carboxyl group that can be cleaved under physiological conditions or a group of the partial formula -N(R_4,R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl or in which R_4 represents hydroxy or esterified hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl; or
(b) R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl;
R_2 represents esterified hydroxy; and
R_3 represents C_1-C_4 alkoxy; or
(c) R_1 represents halogen, hydroxy or C_1-C_4 alkoxy;
R_2 represents hydroxy; and
R_3 represents C_1-C_4 alkoxy; and salts thereof.

3. A compound of the formula (I) according to any one of claims 1 to 2 in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents

hydroxy or esterified hydroxy; and R_3 represents etherified hydroxy or a group of the partial formula -N(R_4,R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl, and salts thereof.

4. A compound of the formula (I) according to any one of claims 1 to 2 in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy or esterified hydroxy; and R_3 represents a group of the partial formula -N(R_4,R_5) in which R_4 represents hydroxy or esterified hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl, and salts thereof.

5. A compound of the formula (I) according to any one of claims 1 to 2 in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy or esterified hydroxy which is cleavable under physiological conditions; and R_3 together with the carbonyl group to which it is attached, represents esterified carboxy which is cleavable under physiological conditions, and salts thereof.

6. A compound of the formula (I) according to any one of claims 1 to 2 in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy or esterified hydroxy which is cleavable under physiological conditions; and R_3 represents a group of the partial formula -N(R_4,R_5) in which R_4 represents hydroxy or esterified hydroxy which is cleavable under physiological conditions, and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen and R_6 represents a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl or in which X is oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl; and salts thereof.

7. A compound of the formula (I) according to any one of claims 1 to 2 in which R_1 represents hydrogen, R_2 represents hydroxy, and R_3 together with the carbonyl group to which it is attached, represents esterified carboxy which is cleavable under physiological conditions, and pharmaceutically acceptable salts thereof.

8. A compound of the formula (I) according to any one of claims 1 to 2 in which R_1 represents hydrogen, R_2 represents hydroxy, and R_3 represents a group of the partial formula -N(R_4,R_5) in which R_4 represents hydroxy and R_5 represents C_1-C_4 alkyl, and pharmaceutically acceptable salts thereof.

9. A compound according to claim 1 selected from the group consisting of Pivaloyloxymethyl-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-carboxylate; N-methyl-2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4 (S)-hydroxamic acid and 2-(3'-hydroxypyrid-2'-yl)-Δ^2-thiazoline-4(S)-hydroxamic acid.

10. An optically pure compound of the formula (I) according to any one of claims 1 to 9.

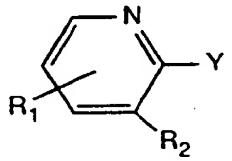
11. An alkali or an alkaline earth metal salts of 2-(3'hydroxypyrid-2'-yl)-2-thiazoline--4(S)-carboxylic acid.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or of an alkali or an alkaline earth metal salts of 2-(3'hydroxypyrid-2'-yl)--2-thiazoline-4(S)-carboxylic acid according to claim 11..

13. A method of treatment of pathological conditions in a mammal that are associated with an excess of trivalent metal ions in the body, comprising administering to said mammal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1.

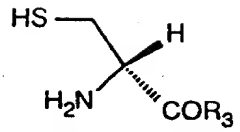
14. Process for the production of a compound of the formula (I) according to claim 1 comprising

a) reacting a picolinic acid derivative of the formula (II)



(II)

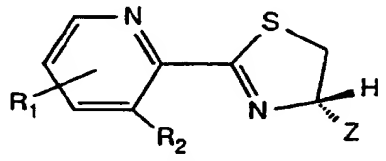
in which R_1 represents hydrogen, halogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkyl; R_2 represents hydroxy, esterified or protected hydroxy and Y represents carboxy or a reactive functional derivative of a carboxy group, with a cysteine derivative of the formula (III)



(III)

in which R_3 represents etherified hydroxy or a group of the partial formula -N(R_4,R_5) in which R_4 and R_5 independently from each other represent hydrogen or C_1-C_4 alkyl or in which R_4 represents hydroxy, esterified or protected hydroxy and R_5 represents hydrogen, C_1-C_4 alkyl or a group -X-R_6 in which X is C_2-C_{12} alkylen or oxaalkylen having 4-12 chain members and R_6 represents C_1-C_2 alkyl or a hydroxylamino group -N(OH)-R_7 in which R_7 represents C_1-C_4 alkanoyl and the hydroxy group is optionally protected, or with a reactive functional derivative of said cysteine derivative (III), or,

b) in a compound of the formula (IV)



(IV)

in which R_1 and R_2 have the above meanings and Z is a carboxy group or a reactive functional derivative thereof, converting the radical Z into a group of the partial formula -COR_3 in which R_3 has the above meanings,

and, if required, splitting off optionally present protecting groups, and/or, if desired, in a resulting compound of the formula (I) in which R_1 and/or R_2 and/or R_4 represent hydroxy, converting said hydroxy into esterified hydroxy, and/or, if desired, converting an obtainable compound of the formula (I) in which R_3 represents etherified hydroxy into a compound of the formula (I) in which R_3 represents a group of the partial formula -N(R_4,R_5), and/or converting an obtainable free compound of the formula (I) into a salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 93/10936

A. CLASSIFICATION OF SUBJECT MATTER

C 07 D 417/04,A 61 K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C 07 D 417/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0 045 281 (CIBA-GEIGY) 03 February 1982 (03.02.82), claims 1-22 (cited in the application).	1-14
X,P	CHEMICAL ABSTRACTS, vol. 119, no. 3, issued July 19, 1993, (Columbus, Ohio, USA) BERGERON, RAYMOND J. et al. "A comparative study of the iron-clearing properties of desferrithiocin analogs with desferrioxamine B in a Cebus monkey model." page 63, column 1, abstract--no. 20 292a & Blood 1993, 81(8), 2166-73 (Eng.).	1

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 February 1994	- 9. 03. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	HAMMER e.h.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/10936

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

"Remark:" Although claim 13 is directed to a method of treatment of diagnostic method practised on a human/animal body (Rule 39.1(iv) PCT) the search has been carried out. Relevant documents are listed within the search report.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANHANG — ANNEX — ANNEXE

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

to the International Search Report to the International Patent Application No.

au rapport de recherche international relatif á la demande de brevet international n°

PCT/US 93/10936 SAE 82190

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les reseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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